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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/703,350	10/31/2000	Fuad Mehraban	10716-15 (CURA-90/P1891R1	3065

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EXAMINER	
YAO, LEI	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/703,350	MEHRABAN ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56 and 69-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56 and 69-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Re: Mehraban *et al.*

Date of priority: 11-01-1999

Request for Continued Examination

The request filed on 02-01-2006 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/703350 is acceptable and a RCE has been established. An action on the RCE follows.

Claims 56, and 69-76 are pending and are currently under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Specification

The specification is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (i.e., see page 32, line 32). Applicant is requested to delete all embedded hyperlinks and/or other forms of browser-executable code. See MPEP §608.01.

Rejection Maintained:

Claims 56, and 69-76 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record in the Action mailed 08-10-2005.

Applicants appear to state (Response, page 2) that the amendment to Claim 56 obviates the rejection, however applicants offer no rationale under 35 USC 112, 1st paragraph.

Thus, to address newly amended claim 56, the claim(s) still fail to provide a written description for the large genus of immunogenic fragments comprising at least 30 consecutive amino acid sequences of SEQ ID NO:76. While Claim 56 recites that the fragment "can generate or select an antibody that specifically binds the polypeptide comprising the amino acid sequence of SEQ ID NO:76", said recitation does not provide a written description for the genus because the possible generation of antibodies or selecting antibodies is not specific to the genus. In other words, because the genus is highly variant, the mere generation of antibodies fails to distinguish the claimed immunogenic fragments from other in the genus. There are potentially hundreds of immunogenic fragments of SEQ ID NO:76 that may or may not be capable of generating antibodies that bind to SEQ ID NO:76. Hence, one of ordinary skill in the art would not recognize that applicants were in possession of the genus of immunogenic fragments. Thus, applicant's arguments have not been found persuasive, and the rejection is maintained.

New Rejections:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 56, and 69-76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are broadly drawn to a method of inhibiting angiogenesis in a mammal comprising administering to the mammal an effective amount of an antibody or antigen binding fragment thereof that specifically binds and neutralizes a polypeptide comprising SEQ ID NO:76 or binds to an immunogenic fragment of SEQ ID NO:76.

The specification teaches that SEQ ID NO:76 is a secreted glycoprotein referred to as a stanniocalcin precursor (page 25). The specification proposes that "neutralizing antibodies to stanniocalcin may be useful as therapeutic molecules because they bind to stanniocalcin and thereby remove it from the immediate cellular environment". Thus, the specification appears to broadly claim that the claimed antibodies would predictably provide a therapeutic benefit to humans in need of reducing angiogenesis. For example, the specification teaches that angiogenesis is an important component of a variety of diseases and disorders including tumor growth and metastasis, rheumatoid arthritis, psoriasis, diabetic retinopathy, neovascular glaucoma, etc. (page 12). Thus, the claims broadly encompass methods of treating cancer by administering an antibody that binds to SEQ ID NO:76.

However, the specification lacks critical guidance and objective evidence to predictably enable those of skill in the art to practice the invention with success. For example, there is no evidence that inhibition of stanniocalcin activity or removal of the secreted glycoprotein of SEQ ID NO:76 results in the inhibition of angiogenesis with concomitant reduction of tumor cell growth in a mammalian subject. There is no guidance that selective binding of SEQ ID NO:76 with an antibody would predictably reduce tumor cell growth or metastasis in a mammalian subject. The state of the art of reducing tumor cell growth and inhibiting other disorders associated with angiogenesis is highly unpredictable.

For example, it was recently revealed that the drug Endostatin is unlikely to be the kind of across-the-board cancer cure that many had hoped for. Out of the 61 terminally ill patients tested, not one recovery had been seen (MSNBC News Services, "Mixed results on new cancer drug", November 9, 2000). Thus, just with regards to inhibiting angiogenesis in general, there is

a high standard of accountability recognized by those in this particular area. Based on the very little guidance in the specification, one of skill in the art would not immediately presume that the antibodies would successfully reduce angiogenesis.

Moreover, the pharmaceutical administration of antibodies for the treatment of tumors requires a high degree of guidance as those of skill in the art recognize the unpredictability of treating mammals (including mammals with tumors) via the administration of antibodies. Jain (Scientific American July 1994), discloses several barriers to the delivery of drugs into solid tumors including large molecular weight drugs such as antibodies. The impediments include (1) Non-uniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, **such as antibodies**, into tumors (page 61, Col. 1 paragraph 1); (4) Convection is a necessary mechanism by which larger therapeutics molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62 col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) Molecules as large as antibodies (i.e., MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2). Further, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents

including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy. Thus, despite evidence that expression of the stanniocalcin gene is upregulated under endothelial tube-forming conditions, the specification offers no guidance and or objective evidence that "inhibiting" or neutralizing this activity in a mammal would effectively inhibit angiogenesis.

In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable that the method would function as contemplated. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

All other rejections and or objections are withdrawn in view of applicant's amendments and/or arguments there to.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 571-272-0835. The examiner can normally be reached on M-Th, 8:30-5:30; alternate Fri., 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gary B. Nickol Ph.D.
Primary Examiner
Art Unit 1642

GBN

GARY B. NICKOL, PH.D.
PRIMARY EXAMINER